EUROPEAN HEMATOLOGY ASSOCIATION

haematologica

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EHA Scientific Conference on Bleeding Disorders
Barcelona, Spain, September 14-17, 2016

ABSTRACT BOOK

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About EHA

The European Hematology Association (EHA) is a non-profit scientific association that represents European medical professionals with an active interest in hematology.

The Annual Congress, organized in a major European City, offers the opportunity to learn about new data from basic, translational and clinical research and gives access to knowledge that directly impacts the clinical practice. Not only the size of the congress increased over the years but also the first steps towards creating an education and career development program were taken.

Educational needs are the focus of our continuing medical education program. Not only through live events, but also through the EHA Learning Center, EHA's official learning platform.

EHA offers education and training and supports the careers of hematologists in Europe and travelling to Europe through its fellowships and grants program. Different fellowships are available for basic, translational and clinical research both in their early or advanced career.

As the largest organization of hematologists in Europe, EHA has taken it upon itself to serve and further their political interests. We advocate for you on the EU level for more research funding, improved research environment and better access to hematology care.

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The EHA Scientific Conference on Bleeding Disorders is organized by:

the European Hematology Association, together with the SWG Bleeding and Thrombosis and the SWG Thrombocytopenia and Platelet Function Disorders. EHA would like to thank both Scientific Working Groups, their chairs and members, and the Scientific Program Committee for their time and effort in organizing this meeting and reviewing the abstracts.

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Word of Welcome

On behalf of the Scientific Program Committee, we are pleased to introduce the Abstract Program for the EHA Scientific Conference on Bleeding Disorders.

The Scientific Program Committee has compiled an exciting program of parallel oral and poster sessions. At least four members of the Scientific Program Committee have reviewed each abstract.

The twelve best abstracts, selected for oral presentation, will be presented during two parallel sessions on Thursday morning. The topics of these sessions are 'Inherited and acquired disorders of platelets' and 'Inherited and acquired coagulation disorders'.

Selected posters can be viewed in the poster area, and will be presented during the Poster Session on Friday afternoon allowing more time for discussion of results and conclusions.

All abstracts selected for oral and poster presentations are also available on the EHA Learning Center: learningcenter.ehaweb.org.

Thank you for your interest in this meeting. We hope that this book will be a valuable source of information and references for you.

Prof Carlo Balduini

Chair EHA SWG on Thrombocytopenias and platelet function disorders

Prof Anna Falanga

Chair EHA SWG on Bleeding and thrombosis

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The origin of a name that reflects Europe's cultural roots.

Ancient Greek

αἷμα [haima] = blood
αἵματος [haimatos] = of blood
λόγος [logos]= reasoning

Scientific Latin

haematologicus (adjective) = related to blood

Scientific Latin

haematologica (adjective, plural and neuter, used as a noun) = hematological subjects

Modern English

The oldest hematology journal,
publishing the newest research results.
2015 JCR impact factor = 6.671

Haematologica, as the journal of the European Hematology Association (EHA), aims not only to serve the scientific community, but also to promote European cultural identify.

PARALLEL SESSION

1A Inherited and acquired coagulation disorders

O01
HEMOSTATIC PROFILE BY ROTATIONAL THROMBOELASTOMETRY (ROTEM) IN SURGICAL CANCER PATIENTS UNDERGOING HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Russo, L.[1] Gamba, S.[1]; Marchetti, M.[1]; Tartari, C.J.[1]; Milesi, V.[1]; Verzeroli C.[1]; Giaccherini C.[1]; Magnone S.[2]; Ansaloni L.[2]; Falanga A.[1]

[1]Division of Immunohematology and Transfusion Medicine - ASST Papa Giovanni XXIII, Italy; [2]Division of Surgery - ASST Papa Giovanni XXIII, Italy

Background
Peritoneal carcinomatosis, a condition characterized by widespread tumor metastases in the peritoneal cavity, occurs frequently in gastrointestinal (GI) and ovaric (OV) carcinomas. Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising treatment protocol; however, it is frequently associated with a hemostatic derangement and a significant blood loss requiring intensive blood transfusion.
Aim
Our aim was to prospectically characterize the hemostatic global profiles of patients with peritoneal carcinomatosis before and during CRS and HIPEC procedures, as measured by ROTEMTM, prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen. The relation of these parameters with blood loss was also evaluated.
Material and methods
Twenty-six cancer patients (15 GI, 11 OV) with a median age of 55 years (range: 35-72 years) were recruited at our Institution, after informed consent. Venous blood samples were collected before surgery (=T0), after CRS (=T1) and after HIPEC (=T2). Thromboelastometry was performed using EXTEM and FIBTEM reagents, to evaluate extrinsic coagulation pathway and fibrinogen concentration. Clotting time (CT, time to clotting initiation), clot formation time (CFT, time of clot increase from 2mm to 20mm above baseline) and maximum clot firmness (MCF, maximum tensile strength of the thrombus) were evaluated.
Results
Before surgery, patients showed significantly ($p<0.005$) higher PT ratio and higher fibrinogen levels than healthy subjects. According to ROTEM analysis, all patients displayed parameters within the normal range values, however the patient group showed a prolonged ($p<0.005$) CT in both EXTEM and FIBTEM tests compared to controls. In addition, MCF was significantly higher in patients compared to healthy controls ($p<0.001$) in FIBTEM test only. After CRS, at T1, fibrinogen levels significantly ($p<0.005$) dropped, and the PT ratio further increased, while no changes were observed for aPTT. Finally ROTEM data showed a significant ($p<0.001$) prolongation of CFT and decrease of MCF values. At T2, after HIPEC, the PT ratio further increased, while fibrinogen level remained unchanged compared to T1. At the same time point a significant reduction of the MCF occurred in both EXTEM and FIBTEM tests. During the procedure 1 patient had severe and 4 had minor bleeding complications.
Conclusions
Treatment of peritoneal carcinomatosis with CRS and HIPEC is associated to a reduction in fibrinogen levels and a pro-hemorrhagic profile. These alterations appear after CRS and worsen after HIPEC. Due to the small number of patients we could not find a correlation with bleeding events or transfusion needs, however our data show that ROTEM may be a promising test to evaluate the perioperative bleeding risk in these patients.

O02
JOINT OUTCOME AFTER JOINT BLEEDS IN PATIENTS WITH VON WILLEBRAND DISEASE COMPARED TO HEMOPHILIA A

van Galen K.[1]; Timmer M.[1]; de Kleijn P.[1]; Leebeek F.[2]; Schutgens R.[1]; Fischer K.[1]; Mauser-Bunschoten E.[1]

[1]UMC Utrecht Van Creveldkliniek, Netherlands; [2]Erasmus MC Rotterdam Hematology, Netherlands

Background
Recurrent joint bleeds are the main cause of joint deterioration (hemophilia arthropathy) in patients with hemophilia. It is unknown to what extent arthropathy occurs following joint bleeds in patients with Von Willebrands disease compared to hemophilia.
Aims
The primary objective was to compare joint outcome by physical examination between adult patients with VWD and moderate and severe hemophilia A (HA) and a history of joint bleeds. The secondary objective was to compare radiological joint damage between these groups.
Methods
Patients with VWD (VWF activity <30%) or moderate or severe HA, who had a medical history of treatment for joint bleeds, were selected for this preliminary analysis. To compare joint outcome we used the Hemophilia Joint Health Score (HJHS range 0-124, obtained by physical examination) and X-ray Pettersson scores (PS range 0-13 per joint) of ankles, knees and elbows. Data on HA were derived from three previous studies. Univariate analyses were performed using Mann Whitney U and Chi2. For multivariate analysis we performed negative binomial regression analysis (HJHS) and logistic regression (dichotomized PS>3).
Results
47 pts with VWD (mean age 45 yrs) were compared to 36 patients with moderate HA (mean age 38 yrs) and 59 patients with severe HA (mean age 26 yrs). More than 5 joint bleeds had occurred more often in the HA patients (27/48 VWD vs. 30/39 moderate HA vs. 58/59 severe HA, $p<0.001$). Joint dysfunction at physical examination was comparable between the patients with moderate HA and VWD (median HJHS 5 in VWD, compared to 5.5 in moderate HA, $p=0.60$ adjusted for age) and slightly worse in severe HA (median HJHS 9, $p=0.02$ compared to VWD and adjusted for age). In moderate HA insufficient X rays were available for the analysis. Apparent joint damage on X rays (PS>3) occurred significantly more often in severe HA compared to VWD (joints with PS>3: 27/40 severe HA vs. 12/46 VWD, OR 11, 95%CI 3-40, $p<0.001$ adjusted for age).
Conclusions
Joint function according to the HJHS in patients with a history of treatment for joint bleeds was comparable between patients with VWD and moderate HA but slightly worse in those with severe HA. Patients with severe HA more often had apparent X ray joint damage. Knowledge of similarities and differences in joint outcome between VWD and hemophilia can be helpful to improve the awareness and treatment of joint bleeds in VWD to prevent arthropathy.
These preliminary data have not been published or presented before.

O03
INCREASE OF MICROPARTICLES TF/TFPI PROCOAGULANT RATIO IN CARRIERS OF INHERITED BLEEDING DISORDERS

Campello E.; Spiezia L.; Radu C.M.; Bulato C.; Saggiorato G.; Sartorello F.; Maggiolo S.; Simioni P.

University of Padua, Italy

Background
Microparticles (MPs) are small membrane vesicles constitutively released from the surface of cells after activation/apoptosis. The best established property of MPs is their ability to promote coagulation, which is largely linked to: i) the presence of phosphatidylserine (PS) on the outer membrane, and ii) the possible presence of tissue factor (TF) on it. Although the presence of MPs has been widely described in hypercoagulable states, their role in hemorrhagic disorders has been poorly evaluated.
Aim
To evaluate the presence and impact of prothrombotic MPs in several congenital bleeding disorders.
Methods
Fifty-three consecutive patients referred to our Unit between 2015 and 2016 who were identified as carriers of inherited bleeding disorders [M/F 30/23; median age 22 years, 12(22%) with hemophilia A, 2(4%) with Hemophilia B, 12(22%) with factor VII deficiency, 8(15%) with FXII deficiency, 6(11%) with FV deficiency, 8(15%) with hypo/dysfibrinogenemia, and 5(11%) with FXIII deficiency] were enrolled. Exclusion criteria were: acute infections, pregnancy/hormonal therapy, cardiovascular diseases, recent surgery, cancer, presence of inhibitor. All samples were performed prior to any administration of factor replacement therapy or plasma. Twenty-six healthy volunteers (M/F 31/25; median age 44 years), friend or companions unrelated to the cases were used as controls. MPs expressing PS, TF-bearing MPS (TF+MPs) and TF pathway inhibitor-bearing MPs (TFPI+MPs) were measured by flow-cytometry using anti-Annexin V-FITC, anti-CD142-PE and anti-TFPI-PE monoclonal antibody, respectively. The ratio of the TF/TFPI expression levels was then used as an index of the procoagulant potential of the MPs and compared between cases and controls.
Results
Overall considered, patients with congenital bleeding disorders showed significantly higher median levels of Annexin V-MPs (3608 [1666-5750] MPs/uL) than healthy controls (2042 [985-3853] MPs/uL, p=0.04). The levels of TF+MPs and TFPI+MPs did not differ significantly between cases and controls. However, the ratio TF/TFPI MPs was significantly higher in cases (1.17 [0.9-1.4]) than in controls (0.94 [0.85-1.13]). Carriers of FVII deficiency and hypo/dysfibrinogenemia showed significantly reduced levels of TFPI+MPs (p=0.002) and a significantly increased TF/TFPI MPs ratio (p=0.019) than healthy controls. Carriers of FXII deficiency showed significantly higher median levels of Annexin V-MPs (p=0.035) and a significantly increased TF/TFPI MPs ratio (p=0.015) compared to healthy subjects. Conversely, carriers of FV deficiency (two of them omozygotes) showed significantly reduced levels of all MPs considered and a significantly reduced ratio (p=0.04) compared to controls. FXIII deficiency carriers (one of them omozygote) presented higher Annexin V-MPs (p=0.0139) median levels and a significant reduction of TF/TFPI MPs ratio (p=0.02) compared to controls. Finally, patients with Hemophilia A and B showed significantly higher levels of Annexin V-MPs (p=0.002) and no difference in other MPs subtypes compared to healthy subjects.
Conclusions
Our study showed that patients with congenital bleeding disorders had an increase TF/TFPI MPs ratio due to reduced levels of TFPI+MPs. MPs may constitute a sort of procoagulant "rescue" mechanism that contribute to inhibit the TFPI pathway and protect carriers of bleeding diathesis. Our results need to be confirmed by larger studies.

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O04
PLATELET AND PLASMA FACTOR XIII LEVELS AFTER REPLACEMENT THERAPY IN SEVERE CONGENITAL FACTOR XIII DEFICIENCY: IS THERE A ROLE FOR FACTOR XIII UPTAKE BY MEGAKARYOCYTES?

Radu C.M.; Bulato C.; Campello E.; Sartorello F; Zanon E.; Milan M.; Gavasso S; Spiezia L.; Simioni P.

University of Padua, Italy

Background
Factor XIII (FXIII), the fibrin stabilizing factor, is involved in the formation of a normal blood clot and is present both in plasma and platelets. Megakaryocytes themselves can synthetize FXIII but is still unclear whether platelet FXIII may derive from endocytosis of exogenous FXIII by megakaryocytes.
Aims
To evaluate plasma and platelets FXIII levels at different time points in a patient with severe FXIII deficiency under replacement therapy with recombinant (r)FXIII concentrates. To investigate the possible *in vitro* uptake of FXIII by megakaryocytes derived from the patient with severe FXIII deficiency.
Methods
Plasma levels of FXIII activity and antigen, as well as intraplatelet content, were measured before and after administration of rFXIII concentrate at different time points. Clot formation was evaluated by whole blood rotational thrombelastometry (ROTEM®) before and after replacement therapy. Synthesis and uptake of FXIII by megakaryocytes in culture were studied by immunofluorescence technique.
Results
Before administration of rFXIII concentrate, plasma FXIII activity and antigen levels were <5% and <1%, respectively. These values increased up to 106% and 77%, respectively, 2 hours after rFXIII administration. Subsequentely, a progressive reduction of both levels up to 32% and 24%, respectively, were seen at day 13 after infusion. Platelet FXIII antigen levels were <1% before replacement therapy and reached 6% within 13 days after infusion.
Coagulation profile in INTEM and EXTEM assays on blood samples collected before replacement therapy, showed a prolonged clot formation time (CFT), reduced clot stability (MCF and AUC) and early clot lysis (ML). Normalization of ROTEM® parameters was seen after administration of rFXIII concentrate.
Cultured megakaryocytes from the patient, before undergoing replacement therapy, were negative for the immunostaining with anti-FXIII antibody and became positive only after the addition of FXIII to the culture medium.
Conclusions
Administration of rFXIII concentrates in severe FXIII deficient patient's results in restoration of FXIII plasma levels and increased intraplatelet FXIII content. Correction of clot formation and stability can be monitored by ROTEM® after rFXIII concentrates. *In vitro* experiments on cultured megakaryocytes from the patient revealed that these cells, which were unable to synthesize FXIII because of a genetic defect, can endocytose exogenous FXIII and possibly produced FXIII-containing platelets, as shown with the *in vivo* data. The role of intraplatelet FXIII still remains to be fully elucidated.

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O05
DATA FROM THE AUSTRIAN HAEMOPHILIA REGISTRY

Rejtő J.[1]; Reitter-Pfoertner S.[1]; Kepa S.[1]; Oberbichler S.[2]; Schuster G.[3]; Streif W.[4]; Male C.[5]; Muntean W.[6]; Hoerbst A.[2]; Pabinger I.[1]

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Background
The Austrian Haemophilia Registry is a web-based patient registry, which was initiated in 2007.
Aims
The primary aim of the Registry is to assess the frequency and the demographic characteristics of patients with congenital bleeding disorders. Secondary aims are to evaluate the treatment modalities and the potential side effects.
Methods
The Registry consists of three parts – part 1 and 2 containing data for quality control and assurance (this data is entered for all known patients); part 3 containing more detailed, patient-specific data (this data is only entered upon written informed consent of each patient). The presented data covers all patients who are treated at the eight Austrian haemophilia treatment centers. Summarized data are presented as percentage values or median and range, as appropriate.
Results
The total number of haemophiliac patients included in the Registry at the end of January 2016 was 753; thereof 635 patients (84%) suffer from haemophilia A (HA), and 118 (16%) have haemophilia B (HB). Patients have a median age of 34 years (range: 1-93 years). Children (under the age of 18 years) represent 20% and adults represent 80% of the population. In the study population, 39% have severe (defined as factor VIII or IX levels <1%), 11% have moderate (factor levels of 1-5%) and 50% have mild (factor levels of 5-50%) haemophilia. The age at diagnosis was available in 84% of the patients. Patients who suffer from the severe form of the disease are typically diagnosed shortly after the first year of life, whereas non-severe patients were most likely to be diagnosed after the age of 4 years (with a median of 7 years of age). Data is available on the treatment modalities of 94% of the patients included in the database: prophylaxis is applied in 71% of the patients with severe haemophilia, whereas 29% receive on demand treatment. The number of severe haemophiliacs on prophylaxis was higher among children (91%) than among adults (62%). Regarding the type of product, 71% of all patients with severe haemophilia have a recombinant product. In 72% of all severe HA patients, a recombinant product is used, whereas this percentage is only 62.5% in severe HB patients. Data on the viral status is available of 71.4% of the patients with severe haemophilia. Overall, 13% of all patients with severe HA are infected with HIV and 37% are HCV-positive; a co-infection with both, HIV and HCV, has been confirmed in 10.7%. Severe HB patients were HIV-positive in 4%, HCV-positive in 37.5% and in 4% a co-infection with HIV and HCV was present. Currently, 3.6% of all HA and 7.8% of the severe HA patients have an inhibitor – 52% of all HA patients with inhibitor and 57% of the severe HA patients with inhibitor have high-titer inhibitor (>5.0 Bethesda Units (BU)/mL). Presently 0.8% of all our HB patients and 4% of severe HB patients have a low-titer inhibitor (<5.0 BU/mL).
Conclusions
The Austrian Haemophilia Registry enables us to obtain epidemiological data on haemophilia in Austria. The Registry also supports us in the effective planning of our scientific projects concerning bleeding disorders.

Reference

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O06
THE INFLUENCE OF COAGULATION FACTORS ON THROMBIN GENERATION IN SOLID TUMOUR AND HEMATOLOGIC CANCER CELLS BY CALIBRATED AUTOMATED THROMBOGRAPHY

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Background
The calibrated automated thrombogram (CAT) assay is emerging as a reliable tool for real time estimation of thrombin generation (TG) potential. There is limited knowledge about the differences in the pathways that underlie the thrombotic phenotype in the solid versus haematological malignant condition. Few studies have investigated the contribution to thrombosis of different factors of the coagulation cascade[1]. Characterizing the TG capacity in these two distinct cancer models using factor deficient plasma might potentially allow better characterization of the thrombotic risk and individualization of prevention strategies.
Methods
Solid tumour cells (pancreatic cancer AsPC-1, CFPAC-1, PANC-1, MIA PaCa-2 and others such as SKOV-3 ovarian cancer, UMSCC81B Head & Neck squamous cancer, PC9 lung cancer) and malignant haematological cell lines (Multiple myeloma MM1.S, U266B, H929 and others including JJN3 plasma cell leukaemia, U937 histiocytic lymphoma) were evaluated at increasing cell concentrations on a Thrombinoscope for the CAT assay, with the addition of platelet-free normal plasma (NormTrol) or plasma deficient in coagulation factors VII and XII, and TF 1pM standard preparations as control. In addition, tissue factor (TF) cell surface expression was measured with flow cytometry.

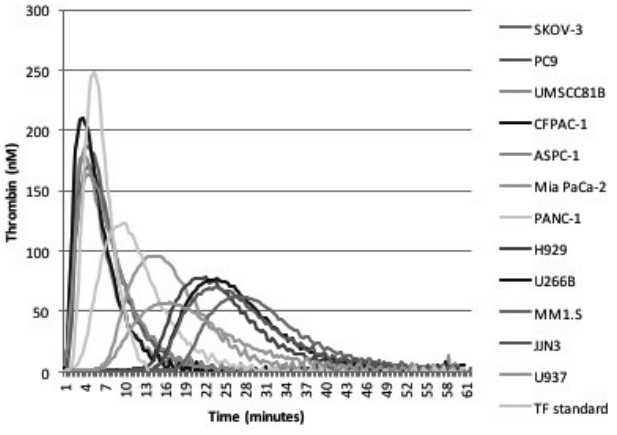

Figure 1. Thrombin generation curves of cancer cells. Thrombograms show TG in NormTrol platelet-free plasma induced by 12 cancer cell lines with low 1pM TF as control.

Results

In NormTrol plasma, TG in all cancer cell lines was concentration dependent, with CFPAC-1 producing the highest thrombin. Absence of Factor-VII in platelet-free plasma resulted in significantly higher inhibition of TG in solid cancers compared to haematological cancers (Figure 2). TF surface expression correlated strongly with the TG parameters e.g. the higher the TF expressed in a cell line, then the shorter the Lag time and time-to-peak, and UMSCC81B expressed the highest TF. Compared to 1pM TF control, solid tumour cell lines had higher thrombin peaks, faster lag times, and a TG profile of overall greater magnitude than haematological cell lines.

Results are mean of n=4 +/- S.D performed in duplicates. *P values from two-way ANOVA are between NormTrol and Factor VII-deficient plasma as those between NormTrol and Factor XII-deficient plasma are mostly insignificant.

Conclusions

This study shows that the specific coagulation factors present in the intrinsic or extrinsic arms of the clotting cascade have a markedly different contribution to the thrombin generation profile of hematologic versus solid malignancies as measured by the CAT assay.

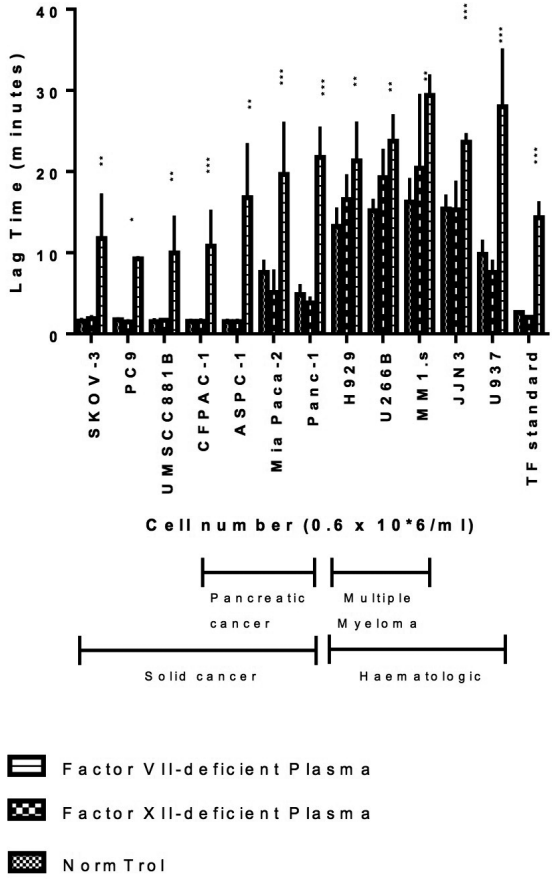

Figure 2. Influence of coagulation factors on thrombin generation in cell lines. TG in solid cancer cell lines was compared with hematologic cell lines *in vivo* on the CAT assay, at 0.6x10^6/mL concentration. Results are mean of n=4 +/- S.D performed in duplicates. *P values from two-way ANOVA are between NormTrol and Factor VII-deficient plasma as those between NormTrol and Factor XII-deficient plasma are mostly insignificant.

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PARALLEL SESSION

1B Inherited and acquired disorders of platelets

O07
MEGAKARYOCYTE AND PLATELET DYSFUNCTION IN PLATELET-TYPE VON WILLEBRAND DISEASE

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Background

Platelet-type von Willebrand disease (PT-VWD) is a rare inherited autosomal dominant bleeding disorder characterized by enhanced platelet GPIbα–von Willebrand factor (VWF) interaction and thrombocytopenia[1]. The bleeding tendency is considered to be due to thrombocytopenia and by the reduction of high-molecular-weight-VWF multimers consequent to the clearance of VWF-platelet complexes from the circulation but no conclusive evidence of this is available.

Aims

Aim of this work was to shed new light on the effects of the enhanced GPIbα-VWF interaction on proplatelet-formation and platelet function in PT-VWD.

Methods

We investigated megakaryocyte differentiation and proplatelet formation in PT-VWD culturing megakaryocytes from CD34$^+$ cells obtained from peripheral blood of a PT-VWD patient expressing the M239V mutation[2] and from bone marrow of a mouse model of PT-VWD expressing the G233V mutation[3]. Platelets from the PT-VWD patient were studied for aggregation and shape change by light transmission aggregometry; for $\alpha_{IIb}\beta_3$ expression and activation (PAC-1 binding), Ca2+ store release and α-granules secretion by flow cytometry; for δ-granules secretion by lumiaggregometry; moreover, platelet spreading on fibrinogen and VWF was assessed and Rap-1b activation (Rap-1b-GTP) and Src-kinase family phosphorylation were measured by Western blotting.

Results

Surface-bound VWF was detected on human PT-VWD megakaryocytes at early stages of differentiation, while only proplatelet-forming megakaryocytes from controls bound VWF. Murine PT-VWD megakaryocytes showed VWF-binding at low doses of ristocetin differently from WT mice. Human PT-VWD megakaryocytes formed long and branched proplatelets on different matrices including type I collagen that usually blocks proplatelet-formation, and showed impaired RhoA activation and myosin-light chain 2 phosphorylation triggered by collagen. Moreover, PT-VWD megakaryocytes migrated through a type I collagen matrix significantly more than megakaryocytes from healthy controls, confirming abnormal interaction with collagen. Bone marrow biopsy from the PT-VWD patient showed an increased number of extravascular platelets in bone marrow. Human platelet aggregation in response to different agonists was reduced and shape change was absent. Human and murine platelets showed defective PAC-1/JON-A binding, Ca2+ release and Rap-1b activation in response to collagen and convulxin, clues of defective $\alpha_{IIb}\beta_3$ activation. Platelet spreading was impaired and Src-family kinase phosphorylation was abnormal, suggesting defective $\alpha_{IIb}\beta_3$ -mediated outside-in signaling.

Conclusions

These results show a primary abnormality of megakaryocyte and platelet function in PT-VWD and demonstrate for the first time that $\alpha_{IIb}\beta_3$ activation and function in platelets are impaired, setting the basis for a full understanding of the bleeding tendency in PT-VWD.

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O08
MOLECULAR CHARACTERIZATION OF GLANZMANN'S THROMBASTHENIA IN IRAN: IDENTIFICATION OF THREE NOVEL MUTATIONS

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Introduction
Quantitative and/or qualitative defects of the platelet membrane glycoprotein (GP) IIb/IIIa complex lead to the clinical entity of Glanzmann's thrombasthenia (GT). A large variety of mutations and polymorphisms are responsible for the aberrant expression and defective activity of this heterodimeric complex. The present study aimed to determine the pattern of GT mutations in Iranian population with GT.

Materials and Methods
We evaluated 20 patients with GT. All exons and splice sites of *ITGA2B* and *ITGB3* were amplified by Touchdown PCR. Mutation screening were analyzed by CSGE heteroduplex PCR and DNA sequencing**.** Immunophenotypic analysis was performed by flow cytometry.

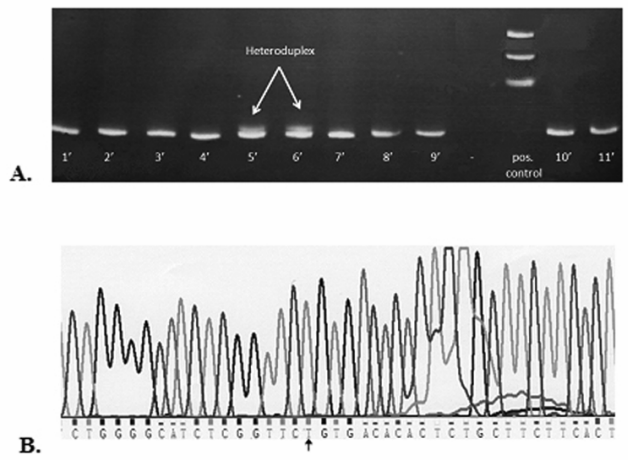

Figure 1. (A) PCR-CSGE of patient 9. Heteroduplex components are seen in gel lanes 5, 6 and positive control lane. Other gel lanes include homoduplex components. **(B)** DNA sequence analysis of *ITGB3*. G- to -A transition at nucleotide 719, changing Arg240 to Gln (R240Q), was detected. This substitution mutation makes a new codon CAG (→). In this picture, due to inserting the sequence of the opposite strand (Reverse), codon CTG (←) is displayed instead of codon CAG(→). The arrow shows the position of the substitution.

We identified three novel mutations, one previously identified mutation and three polymorphisms which two of them were novel. in detailed, one substitution mutation, two deletions of a single nucleotide, one insertion of a single nucleotide, two synonymous polymorphisms and one missense polymorphism were found.

Discussion
All detected mutations were homozygous which likely contribute to the pathogenesis of GT. Furthermore, it suggested *ITGB3* as the mainly affected glycoprotein impaired in the patients with GT. As expected, the molecular results were consistent with the phenotypic findings, so that the GPIIb/IIIa complex was disrupted by mutations in all studied patients with type I GT. Finally, we concluded that intronic alterations or epigenetic regulation is responsible for the aberrant expression and/or defective activity of GPIIb/IIIa complex in the other patients.

Keywords
Glanzmann's Thrombasthenia, ITGA2B, ITGB3, GPIIb/IIIa complex, Novel mutations and polymorphisms.

Table 1.

Description	mRNA	a.a	Codon pos.	DNA	Exon	GP	Gene	HGMD ID
Homo	754	240: Arg? Gln	2	719: G? A (CGG? CAG)	5	IIIa (β3)	ITGB3	CM920386
Homo	-	-	-	1185: Del C	9	IIIa (β3)	ITGB3	HQ288893
Homo	-	-	-	1986: Ins T	12	IIIa (β3)	ITGB3	HQ288894
Homo	-	-	-	113: Del A	1	IIb (α2b)	ITGA2B	HQ285246

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O09
ROMIPLOSTIM IN SPLENECTOMIZED (SPLNX) AND NON-SPLENECTOMIZED (NONSPLNX) PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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Background
ITP is an autoimmune disorder with increased platelet destruction and insufficient platelet production. Romiplostim, a thrombopoietin receptor agonist, improves ITP outcomes compared with control (placebo or standard of care). Splenectomy removes a major site of sequestration of antibody-coated platelets, which might alter responsiveness to romiplostim or increase the risk of thrombosis or other complications. The efficacy and safety of romiplostim in splnx versus nonsplnx patients are not fully characterized.
Aims
This analysis evaluated safety and efficacy for splnx vs nonsplnx patients across 13 completed clinical studies of romiplostim in adults with ITP.
Methods
Data up to June 2014 were pooled. Informed consent was obtained in each ITP study. Safety was analyzed after ≥1 dose of romiplostim or control. Adverse event (AE) rates were adjusted for time of exposure. Efficacy included platelet response (any ≥50x10^9/L) and sustained platelet response (≥50x10^9/L ≥9 of 12 consecutive weeks). Four dose-finding studies that employed off-label doses were excluded from efficacy analyses.
Results
Safety was analyzed for 1111 patients (395 splnx; 716 nonsplnx). At baseline, splnx (vs nonsplnx) patients had longer median ITP duration (8.7 [95%CI: 7.7, 9.7] vs 1.6 [1.4, 2.0] yr), lower median platelet count (14.0 [12.0, 15.3] vs 19.3 [18.0, 21.0] x10^9/L), and a higher proportion with >3 prior ITP treatments (38% [33.2%, 43.0%] vs 12% [9.5%, 14.3%]). Splnx patients used more rescue medications (263.4 [95%CI: 251.5, 275.7] vs 153.3 [125.3, 138.8] per 100 pt-yr). Exposure-adjusted AE rates are provided in the table. AE rates per 100 pt-yr in the control group for both splnx (1861.1 [95%CI: 1616.9, 2132.2]) and nonsplnx (1052.6 [989.3, 1119.0]) patients were higher than in the respective romiplostim group. Efficacy data were analyzed for 1024 patients (376 splnx; 648 nonsplnx). Median platelet counts increased with romiplostim and platelet responses were stable over time in both subgroups. For romiplostim, rates of platelet response (≥50x10^9/L at least once) were 82% (95%CI: 78%, 86%) for splnx and 91% (89%, 93%) for nonsplnx patients (p<.0001), and rates of sustained platelet response (≥50x10^9/L ≥9 of 12 consecutive weeks) were 68% (63%, 72%) and 80% (77%, 83%), respectively (p<.0001).
Summary/Conclusions
Removing a major site of platelet sequestration increased neither responsiveness nor toxicity of the thrombopoietin receptor agonist, romiplostim. In splnx patients, platelet response rates were lower, use of rescue medications was higher, and exposure-adjusted rates of hemorrhage AEs and infection AEs were higher. Differences between splnx and nonsplnx patients in disease duration/severity may have influenced concomitant treatments and safety/efficacy results. In conclusion, romiplostim safety generally was comparable between splnx and nonsplnx patients and platelet response rates were high in both populations.

Table 1. Duration-adjusted AE Rate per 100 pt-yr (95% CI).

	Splnx (702.0 pt-yr)	Nonsplnx (1129.7 pt-yr)
Any AE	1226.4 (1200.6, 1252.5)	851.9 (835.0, 869.1)
Hemorrhage AEs	266.1 (254.2, 278.4)	140.8 (134.0, 147.9)
Infection AEs	156.7 (147.6, 166.2)	124.8 (118.4, 131.5)
Thrombotic AEs	6.3 (4.6, 8.4)	4.6 (3.4, 6.0)
Reticulin AEs*	0.4 (0.2, 7.4)	0.6 (0.2, 1.3)
Any serious AE	68.1 (62.1, 74.5)	44.1 (40.3, 48.1)
Any fatal AE	1.6 (0.8, 2.8)	2.7 (1.9, 3.9)
Any treatment-related AE	123.1 (115.0, 131.6)	82.1 (76.9, 87.6)

**AEs reported as bone marrow reticulin fibrosis, myelofibrosis, or reticulin increase across 12 studies; excluded 1 ITP study specifically designed for bone marrow assessment (reported separately).*

O10
PROGNOSTIC ASSESSMENT IN *MYH9*-RELATED DISEASE: NO LONGER JUST A MATTER OF HEAD OR TAIL

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Background
MYH9-related disease (*MYH9*-RD) is an autosomal-dominant disorder caused by mutations in the gene for non-muscle myosin heavy chain IIA (NMMHC-IIA) and represents the most frequent inherited thrombocytopenia. NMMHC-IIA comprises two distinct domains, the N-terminal globular head domain (HD) and the C-terminal tail domain (TD), and causative mutations hit either the HD or the TD. All patients present at birth with macrothrombocytopenia and only some of them develop during life additional manifestations, including nephropathy often leading to end-stage renal disease (ESRD), sensorineural deafness, and/or cataract. Thus, the search for genotype-phenotype correlations in *MYH9*-RD has been an important research topic since the identification of the disorder. In 2008, the analysis of 108 patients allowed us to conclude that the mutations affecting the HD were associated with evolution to early-onset ESRD and deafness, whereas the risk of non-hematological manifestations was much lower for patients with TD mutations. In 2014, raising to 255 the number of patients, we suggested that evolution to juvenile ESRD associated only with the most frequent among HD mutations, i.e. substitution of the arginine 702 (R702). Conversely, the other HD mutations, which were almost all localized in a distinct hydrophobic region at the interface between the SH3 subdomain and the motor domain (SH3/MD interface), associated with a less severe evolution.
Aims
To improve prognostic assessment of patients with *MYH9*-RD.
Methods
All the consecutive patients enrolled in the Italian registry for *MYH9*-RD until December 2015 were included. The association of *MYH9* genotype with phenotype was assessed by a generalized linear regression model (event-free survival analysis).
Results
We enrolled 350 patients belonging to 199 *MYH9*-RD pedigrees. Mutational screening allowed us to identify 6 novel causative mutations in the HD in 6 different pedigrees. Interestingly, all of these variants were localized in the hydrophobic region at the SH3/MD interface. By raising the number of patients with mutations in this region from 14 to 26 and increasing the observation time, we could demonstrate that mutations in the SH3/MD interface are associated with development of deafness at young-middle age, but low risk of kidney disease and cataract. The other previously identified genotype-phenotype correlations were confirmed. In particular, mutations hitting the R702 in the HD resulted in constant evolution toward juvenile ESRD and severe deafness. Among mutations different from R702 substitutions, the p.D1424H in the TD associated with the highest risk to develop non-congenital manifestations of the disease.
Conclusions
Mutations in the HD of the NMMHC-IIA are almost all localized in a specific region at the SH3/MD interface, which therefore represents a critical region for *MYH9*-RD pathogenesis. Most importantly, patients with HD mutations can be distinguished into two different prognostic groups: subjects with R702 substitutions are expected to early develop a severe syndromic disorder, whereas mutations in the SH3/MD interface are associated with evolution to a milder phenotype, characterized by development of hearing impairment only ("auditory" phenotype). Our study confirmed a genotype-phenotype model for *MYH9*-RD that overcomes the previously reported dualism between HD vs. TD mutation.

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O11
ETV6 RELATED THROMBOCYTOPENIA (*ETV6*RT): A NEW FORM OF INHERITED THROMBOCYTOPENIA PREDISPOSING TO CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Background
In 2015, different studies disclosed that mutations in the gene *ETV6* are responsible for a new form of IT and suggested that *ETV6*-RT predisposes to hematological malignancies[1-2].
Aims
To gain further information on this new IT, in particular on the predisposition to hematological malignancies, in order to reach a clinical and pathogenetic characterization.
Methods
We enrolled 130 unrelated patients with ITs investigated at the IRCCS Policlinico San Matteo Foundation of Pavia, Italy. All of them had no definite diagnosis because they did not fit the criteria for any known IT[3]. They were part of our series of 274 consecutive propositi analyzed in our institution from 2003 to 2014. Whenever *ETV6* mutations were identified, the available relatives of probands were studied. *ETV6* mutations were investigated by WES or Sanger sequencing. Each patient underwent phenotypic characterization (blood cell counts and platelet size; platelet flow cytometry; platelet aggregation; platelet activation; platelet adhesion and spreading; differentiation of human megakaryocytes and morphological analysis; megakaryocyte flow cytometry; evaluation of proplatelet formation by *in vitro* differentiated megakaryocytes).
Results
We identified 20 subjects from 7 families bearing 5 different *ETV6* mutations. The bleeding tendency and the degree of thrombocytopenia were mild, but we found that 4 of 20 patients (20%) had ALL, thus confirming that early leukemic transformation is a major risk of this IT. Moreover, we found that one patient developed *JAK2* positive polycythemia vera at age 37, suggesting that this disease should be added to the list of malignancies to which the *ETV6*-RT predisposes. Our study did not identify any peculiar feature that can be used to raise the suspicion of *ETV6*-RT and the diagnosis is therefore difficult. Moreover, we did not identify any distinguishing defect of major platelet GPs or *in vitro* platelet aggregation. Also evaluation of peripheral blood films did not found any morphological abnormality, apart from platelet anisocytosis and an increased percentage of large platelets, which are common to the majority of ITs. However, at variance with most ITs, MPD and MPV were consistently normal in *ETV6*-RT, and it is just the normal size of platelets that should rise suspicion of this condition in subjects with an autosomal dominant thrombocytopenia. This finding is shared with ITs due to monoallelic mutations in *RUNX1* and *ANKRD26*, which also have normal platelet size and predispose to leukemia. *In vitro* studies revealed that patient megakaryocytes have defective maturation and proplatelet formation, while platelets have reduced ability to spread on fibrinogen, thus suggesting some functional platelets defect. We found also that *ETV6*-RT is relatively frequent: in fact, in our series, *ETV6*-RT had a relative prevalence of 2.9% in the whole case series, and of 4.6% in the series of patients with known ITs. Its frequency was lower only to that of monoallelic BSS, *MYH9*-RT, *ANKRD26*-RT and biallelic BSS.
Conclusions
Monoallelic *ETV6* mutations cause one of the most frequent forms of ITs, without large platelets, and confirmed that affected subjects have high propensity to hematological malignancies, in particular childhood

ALL. Since the only dominant ITs without platelet macrocytosis are *ETV6*-RT, FDP/AML, and *ANKRD26*-RT, we suggest that all subjects with a dominant IT and normal platelet size should be tested for mutation in these genes.

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O12
INFLUENCE OF STORAGE ON HEMOSTATIC PROPERTIES OF PLATELETS FOR TRANSFUSION USE

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Background
Transfusion of platelet concentrates (PC) is extensively used either prophylactically to prevent bleeding in high-risk thrombocytopenic patients, or therapeutically to control active bleeding. A good hemostatic potential of platelets in PC is important for a successful transfusion to obtain an effective and rapid hemostatic action in the recipient. PC standard quality is routinely performed by evaluating platelet and leukocyte counts, swirling, volume, and pH changes; however these parameters are not able to define the platelet hemostatic functionality.
Aims In this study we aim to assess the impact of storage conditions on the hemostatic potential of PC by measuring platelet activation, secretion, and aggregation capacity, both before and after storage.
Methods
Consecutive 70 random PC (O blood group=43, A blood group=27) from 280 blood donors (253M/27F, Median age=41.5 (19-65)) were analyzed at the day of preparation (D0) and after 4 days of storage (D4) at 22°C on lateral agitation. Antigenic levels (i.e ELISA method) of platelet α-granule proteins (*i.e.* platelet factor-4 (PF4), β-thromboglobulin (β-TG), thrombospondin-1 (TSP-1), vascular-endothelial growth factor (VEGF)), soluble P-selectin and, soluble Glycoprotein V (sGPV) in PC supernatants were evaluated as markers of spontaneous degranulation and platelet membrane shedding. PLT aggregation (300,000 plts/ul) was assessed by light transmission aggregometry (LTA; Born method) in response to collagen, thrombin (*i.e.*TRAP-6), ristocetin, or arachidonic acid (AA). Statistical analysis was performed using SPSS statistic data editor.
Results
Levels of α-granule proteins increased during the four days of storage with different trends according to the specific marker; particularly a median increase of 141% for PF4 ($p<0.01$), 110% for β-TG ($p<0.01$), 179% for VEGF ($p<0.01$) and 33% for TSP-1 was recorded. Also levels of soluble proteins (P-selectin and GPV) significantly ($p<0.01$) increased during storage, demonstrating an ongoing shedding of these proteins from platelets. No significant differences between ABO groups were observed concerning the levels of soluble markers. The increased degranulation observed during CP storage was associated to a parallel and significant ($p<0.01$) decrease in the aggregation response of platelets to collagen (-58.5%), TRAP6 (-35%), ristocetin (-22.4%), but not to AA (-8.5%; p=ns). Platelet aggregation was not different between ABO groups, although a trend to decrease was observed in CP from A compared to O blood group at each time points. A significant ($p<0.05$) correlation was found between the relative increase (from T0 to T4) in PF4, β-TG and sGPV levels and the decrease in AA-, TRAP6- and ristocetin-induced aggregation. Best correlations were found between β-TG ($r=-0.544$; $p=0.000$) or PF4 ($r=-0.596$; $p=0.000$) levels and ristocetin-induced aggregation.
Conclusions
During PC storage, platelets change their hemostatic phenotype becoming more activated and less responsive to *in vitro* stimuli by the aggregation assay. This spontaneous phenomenon was observed in all the 70 CP tested during storage independently from ABO group type. Testing platelets for their hemostatic potential could be useful to identify PCs that might not display full functionality and reactivity in the recipient. However, further studies are necessary to investigate the correlation between platelet functionality in PC and the recovery of the hemostatic balance in the transfused recipient.

POSTER SESSION

P01
ABSTRACT WITHDRAWN

P02
ONE BIG PROBLEM SOLVED; MENOMETRORRHAGIA IN FEMALE PATIENTS WITH GLANZMANN THROMBASTHENIA SUCCESSFULLY TREATED WITH NASAL DESMOPRESSIN

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Background
Glanzmann thrombasthenia is a rare genetic platelet disorder in which the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) complex is either dysfunctional or deficient and it is observed more often in populations that consanguinity marriages are more often such as Turkey. Bleeding manifestations may be clinically variable, ranging from easy bruising to severe and potentially life threatening hemorrhages. Menorrhagia is an important bleeding type causing severe anemia among female Glanzmann thrombastenia patients.
Aims
We aimed to document the clinical and laboratory spectrum of our patients with Glanzmann thrombastenia, focus on patients with recurrent menometrorrhagia and their response to nasal desmopressin treatment.
Methods
From January 2002 to December 2015, 34 patients (13 female and 21 male) with Glanzmann thrombasthenia who were diagnosed and followed in Hacettepe University Pediatric Hematology department were retrospectively evaluated through hospital records.
Results
At initial diagnosis patients ages ranged between 2.5 to 180 months (median 36 months) and their first bleeding episode occured between ages 1 to 180 months (median 36 months). Two patients were diagnosed because of a known sibling with this diagnosis and there were consanguinity between parents in 19 patients. Flow cytometry confirmed the diagnosis of Glanzmann thrombasthenia and CD41, CD61 were found to be 0%. Bleeding episodes tend to be mild mucocutaneous bleedings, such as petechia, echymoses, epistaxis and gingival bleeding. Epistaxis was found to be the most common bleeding type (n: 16) however bleedings from other anatomic sites like tonsillary (n:1), gastrointestinal (n:2), hematuria (n:1), hemarthroses (n:1), intracranial (n:1) and menorrhagia (n:3) were observed too. We focused on these 3 patients with recurrent menometrorhagia. One of these 3 patients was hospitalized 3 times for severe anemia because of uncontrolled menorhagia and received rFVIIa. All of these patients took hormonal therapy to control their menometrorrhagia. They were also taking iron replacement therapy. But they were all anemic with hemoglobin values 11 g/dL, 7,4 g/dL, 6,4 g/dL respectively. Nasal desmopressin was started to given during their menstrual bleeding days (2x150 mq/puff) with fluid restriction and 3 months after treatment hemoglobin levels increased found 13,9 g/dL, 10,9 g/dL and 12,7 g/dL respectively. Moreover, hormonal treatment was stopped by administering nasal desmopressin. No side effect was observed. They all declared that their bleeding intensity decreased and duration was shortened.
Summary - Conclusions
Our experience showed that nasal desmopressin treatment is effective and safe to control menometrorrhagia among female patients with Glanzmann thrombasthenia.

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P03
CHARACTERIZATION OF PATIENTS WITH IMMUNE THROMBOCYTOPENIA ENTERING REMISSION IN A ROMIPLOSTIM BONE MARROW STUDY

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Background
The thrombopoietin receptor agonist romiplostim is approved for use in adults with chronic ITP. In this study, patients with ITP (N=169) had bone marrow biopsies performed at baseline and after 1, 2, or 3 years of romiplostim; 24 patients discontinued romiplostim and entered remission.
Aims
To examine remission in patients with ITP receiving romiplostim in a bone marrow study.
Methods
Patients with ITP entering the bone marrow study had a platelet count $<50\times10^9$/L and ≥1 prior ITP therapy. Romiplostim, received weekly for up to 3 years, was adjusted from 1-10 µg/kg to target platelet counts of $50\text{-}200\times10^9$/L; doses were reduced for platelet counts $>200\times10^9$/L for 2 consecutive weeks and no romiplostim was given for platelet counts $>400\times10^9$/L. A *post hoc* analysis was conducted of those who entered remission, ie platelet counts $\geq50\times10^9$/L for ≥6 months with no ITP therapy, including romiplostim.
Results
The median years since ITP diagnosis for those who did (N=24) and did not (N=145) enter remission (1.66 years vs 5.16 years) had overlapping ranges [not significant (NS)], as did the median average weekly dose (1.1 µg/kg vs 3.5 µg/kg, NS, included zero doses prior to last non-zero dose) (Table 1). Adverse events (AEs) occurred at similar rates. A *post hoc* analysis examining the association between remission and baseline factors including age, gender, platelet count, prior splenectomy, ITP duration, and number of prior treatments indicated that ITP duration ≤1 year could be a potential predictor for remission (hazard ratio 2.46, 95% CI: 1.04, 5.79, p=0.04); however, this association could be due to multiple comparisons (ie, type I error). Median time of onset for remission was 52 weeks (range, 6–124 weeks) and median duration of remission during the study was 88 weeks (range, 29–154 weeks); 21 of the 24 patients were still in remission at the last observation on study.
Conclusion/Summary
In this *post hoc* analysis, 14% (24/169) of patients in a romiplostim ITP bone marrow study were able to enter remission following standard dosing rules; more studies are needed to confirm whether shorter ITP duration is a predictor of remission.

Table 1.

Characteristic	Remission (N=24)	No remission (N=145)
Women, n (%)	12 (50)	102 (70)
Age, y, median (Q1, Q3)	45.5 (31.0, 58.0)	51.0 (37.0, 64.0)
Years since ITP diagnosis, median (Q1, Q3)	1.66 (0.46, 7.75)	5.16 (1.62, 12.84)
Prior splenectomy, n (%)	7 (29.2)	53 (36.6)
Platelet count at screening, $\times10^9$/L, median (Q1, Q3)	20.9 (7.5, 35.0)	23.0 (11.0, 35.0)
Time to first platelet response, n, weeks, median (Q1, Q3)	24, 3.5 (2.0, 14.0)	131, 2.0 (2.0, 6.0)
Treatment duration, weeks, median (Q1, Q3)	62.5 (14.1, 82.1)	155.7 (66.0, 156.0)
Average weekly dose, µg/kg, median (Q1, Q3)	1.1 (1.0, 2.2)	3.5 (1.9, 7.2)
Splenectomy on study, n (%)	0	3 (2.1)
Any treatment-related AE, n (%)	9 (37.5)	51 (35.2)
Serious AE / Treatment-related serious AE, n (%)	8 (33.3) / 0	48 (33.1) / 6 (4.1)
Fatal AE, n (%)	0	7 (4.8)
Bone marrow changes (increased reticulin ≥2 grades or collagen), n (%)	0	9 (6.2)
On-study bleeding AE, n (%)	15 (62.5)	84 (57.9)
On-study grade ≥2 bleeding AE, n (%)	4 (16.7)	34 (23.5)
On-study serious bleeding AE, n (%)	1 (4.2)	13 (9.0)

P04

PLATELETS HEMOSTATIC ACTIVITY FALLS IN STORED PLATELETS CONCENTRATES

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Background

Apheresis and storage of platelet concentrates (PCs) affected by the platelets activation and total functional capacity of these cells. We assume that after transfusion the prevalence of platelets with changed activity lead to worse quality of blood clot in vivo. The aim was the in vitro study of platelet-dependent clot properties as a function of storage time.

Methods

Fifty single-donor apheresis PCs were divided in two groups: group 1 - platelets were remained in autologous plasma (PCs-P; n=26); group 2 – platelets were resuspended in platelet additive solution (PAS) which substituted up to 70 vol% of autoplasma (PCs-PAS; n=24). Storage conditions were equal. PCs samples were analyzed by modified thromboelastography, and by aggregometry, and for platelets count, pH, lactate, glucose, and other platelets parameters. The testing were carried out in the day of proceeding, after 24 hours, and at 3rd and 5th days of storage. Dates were present as median (95% CI). Statistical differences were calculated using Mann-Whitney test ($p<0,05$), besides regression analysis was performed.

Results

Between PCs-P and PCs-PAS no significantly differences had for platelets count. From the day of producing to the 5th days of storage glucose decreased in PCs-P from 18,3 mmol/L to 9,4 mmol/L (-48.6%), and in PSc-PAS from 5,2 mmol/L to 1,3 mmol/L (-52%), and lactate concentration had the increase in PCs-P from 2,7 mmol/L to 16,4 mmol/L (6-fold up), and in PCs-PAS from 1,4 mmol/L to 9,6 mmol/L (6,9-fold up). However pH was almost unchanged that indicated buffer conditions were good in both types of PCs. During the storage platelets aggregability and adhesion had worsened independently PCs type. Platelet aggregation decreased in PCs-P from the day of producing to the 5th days of storage ADP-induced by 44%, collagen-induced by 29,5%, ristomycin-induced by 40,4%. In PCs-PAS platelet aggregation decrease in response to ADP, collagen, ristomycin was 44%, 30%, 26%, respectively. We found that clot demonstrated gradual reduction of elasticity and deformability in both PCs groups (in PCs-P: Angle -30%, MA -9%, G -24%; in PCs-PAS: Angle -19%, MA -13%, G -29%). According to regression analysis in PCs-P platelets lost their meaning for clot properties from the third storage day, in PCs-PAS activated platelets had no impact to clot properties during full storage time.

Conclusions

Irrespective of the proceeding method platelets viability was saved during the first five days of storage. Platelets apheresis and storage are accompanied by aggregation-and- adhesion activity depression. It could be speculated that storage impairs platelets granules secretion and thromboxane A2 synthesis, and cell-cell interaction. We found total decline of clot quality including low elasticity and impaired deformability during of storage time. We assume that clot properties are forming at the day of proceeding. Therefore we suppose that effect PCs transfusion is related to successful of platelets activity recovery *in vivo.*

P05

POSTPARTUM HEMORRHAGE IN WOMEN WITH VON WILLEBRAND DISEASE - A RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction

Von Willebrand disease (VWD) is a hereditary bleeding disorder, caused by a deficiency in the levels and/or function of von Willebrand factor (VWF). Women with VWD appear to be at increased risk of experiencing postpartum hemorrhage (PPH), though the levels of VWF increase during pregnancy. There is limited knowledge of how PPH is associated with the subtype of VWD, plasma levels of other coagulations factors than VWF and given hemostatic treatment.

Aims

The aims were to investigate the incidence of PPH in women with VWD and to analyse the correlation between PPH and: (1) type of VWD, (2) laboratory monitoring of VWF and FVIII and (3) hemostatic drug treatment.

Methods

This was a retrospective observational study. The study participants (n=34) were recruited from the Coagulation Unit, Karolinska University hospital. Fifty-nine deliveries occurred in 14 different obstetrics units (years 1995-2012) were included in the study.

Results

The incidence of primary PPH was 44%, severe primary PPH 20% and secondary PPH 12%. VWD type 3 was associated with a higher risk of experiencing severe primary PPH compared to other subtypes. FVIII:C in pregnancy was inversely correlated to blood loss during delivery. There was a significantly higher incidence of secondary PPH when the VWD diagnosis was unknown at time of delivery.

Conclusions

The women with VWD are at higher risk of PPH, especially those with type 3 VWD or when diagnosis is unknown prior to delivery. Identification of pregnant women with undiagnosed VWD may be of importance in order to prevent PPH.

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P06
PLATELET AGGREGATION DEFECTS IN WOMEN WITH ENDOMETRIOSIS

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Objective
To assess the frequency of inherited bleeding disorders in women with endometriosisand to establish if there is an association between coagulation parameters and severity of endometriosis.
Design
A case-control study including women with endometriosis and age-matched controls
Setting
Conducted at the Royal Free Hospital (RFH), north London from July 2013 until July 2014
Population
Case participants were women with a surgically confirmed diagnosis of endometriosis (n=84). Control participants were staff members of the RFH matched by age and ethnicity (n=30).
Methods
All participants were interviewed to complete pain impact questionnaire (PIQ), pictorial blood assessment chart (PBAC), and grade of endometriosis (cases only).Laparoscopic revised American Society of Reproductive Medicine (rASRM) stage ofendometriosis was documented where recorded. Laboratory investigations ofhaemostasis included platelet aggregation testing, and coagulation factor levels (VIII, IX, XI, XIII, von Willebrand factor [VWF]).
Main outcome measure
Frequency of platelet aggregation defects or factor deficiency in women withendometriosis compared to controls. Correlation of factor levels with laparoscopic staging and PIQ score.
Results
Women with endometriosis had significantly more defects of platelet aggregation to one and multiple agonist compared to controls (31% vs 4%, p = 0.005 and 15% vs 4%, p < 0.05, respectively). VWF level demonstrated a significant downward trend with increasing laparoscopic stage (r = -0.35, p = 0.01). Five women with severe endometriosis had a VWF level < 50 IU dL-1.
Conclusions
Endometriosis is associated with platelet aggregation defects. This may have important implications in the treatment of endometriosis.

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P07
PLATELET DYSFUNCTION DURING AND AFTER CARDIOPULMONARY BYPASS DETECTED WITH THROMBELASTOGRAPHY AND PLATELET AGGREGATION ASSAYS

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Cardiopulmonary bypass (CPB) is associated with complex activation of hemostatic system. The complexity of this patterns cannot be described by standard laboratory tests especially during full heparinization. Thrombelastography (TEG) is reliable method for detection of hemostatic abnormalities during surgery. Some limitation of this examination are necessity to know platelet count and function, concentration of fibrinogen, threshold level of ionised calcium and temperature adjustment.
Two groups of elective cardiac surgery patients were evaluated in prospective randomized study. Group TEG (n=499) was monitored both with TEG and laboratory tests (prothrombin time - PT, thrombin time, - TT, activated partial thromboplastin time-aPTT, fibrinogen - FBG, platelet count and function, fibrin degradation products- FDP). Standard ACT (Activated Clotting Time – Hemochron® - kaolin activated) monitoring was provided. Group Control (n=475) was monitored only with laboratory tests. Thrombelastograph TEG®5000 Series (Haemoscope, Niles, IL, USA) was used. Blood was sampled from central venous cathether without heparin flush. Kaolin activated cuvettes were used.The following TEG measurements were performed: 1st after induction of anesthesia (native), 2nd during cardiopulmonary bypass (CPB) after X-clamp releasing (heparinase), 3rd and 4th 10min after protamine administrativ (nativ and heparinase). Hemostatic profile with using TEG algorithm (delivered by manufacturer), changes of TEG parameters and laboratory tests before and after CPB, blood loss, number of transfusion and reexploration because of bleeding were evaluated. Standard dosing of heparin (3mg/kg bolus+1mg/kg to CPB) and no profylactic antifibrinolytics were used. Chronic antiplatelet/anticoagulation drugs were withdrawn according to ESC/ESA guidelines.
Results
Both groups were comparable by demographics (TEG/Control):. Mean age 67,5 vs 68,4. Type of surgery% (CABG 65/73, valvular 17/12, combined 15/13, other 2/1). No difference in CPB parameters (CPB time 80/78 min, total heparin 310/311 mg and protamin 339/339 mg dose). No significant difference in peroperative blood loss (373±351/351±229 ml), number of transfusion (RBC 0,63/0,70 RBC unit/pt, 0,34/0,40 FFP unit/pt, 0,01/0,01 platelet unit/pt), therapeutic antifibrinolytics administration (12/10,7%) and reexploration because of bleeding (1,6%/2,5%) were recorded. The only significant difference in postoperative blood loss (819±519 vs 861±422 ml, p<0,05) was assessed. Values of PT, aPTT, TT significantly increased, fibrinogen and platelets significantly decreased during CPB (212±64 vs 134±44 in TEG, 218±65 vs 139±46 in control). Changes of PT, aPTT and platelets correlated with CPB duration. The main hemostatic patterns according to TEG algorithm: T1: 18,0% platelet hyperfunction, 12,4% enzymatic hypercoagulability. T2: 22,8% platelet hypofunction, 19% primary fibrinolysis. T3: 9,4% platelet hypofunction, 7% primary fibrinolysis. T4: 15,0% platelet hypofunction, 8% enzymatic hypercoagulation.
Conclusions
Platelet decrease is usual during CPB. Platelet hypofunction and primary fibrinolysis were the most common patterns during CPB. We need a new technique to preserve platelets during CPB. One option is using of autologous platelet-rich plasma apheresis before CPB and monitoring their function by aggregation methods.
Acknowledgement
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P08
WHICH TYPE OF FVIII ACTIVITY ASSAY BEST REFLECTS THE "TRUE" POTENCY OF RVIII-SINGLECHAIN?

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Background and Aims
All recombinant FVIII products commercially available so far show more or less distinct differences of the one-stage (OS) clotting and chromogenic substrate (ChS) activity assay ratios when tested against a human plasma-derived FVIII concentrate standard. A good correla-

tion of the molar quantities of several rFVIII products with their corresponding ChS FVIII activity determinations has previously been demonstrated. The goal of the present studies was to assess which of the FVIII activity assay principles best reflects the "true" (=physiologically relevant) potency of a newly developed single-chain rFVIII concentrate (rVIII-SingleChain) as well as considering the diversity of commercially available assay reagents.

Methods

rVIII-SingleChain (Afstyla®), a product of CSL Behring, and X different rFVIII comparator products were investigated. For ChS and OS FVIII activity determinations commercially available reagents and FVIII-depleted plasma were used. Thrombin generation (TG) was performed using PPP-reagent Low (Thrombinoscope) and FVIII-depleted plasma. Blood loss was determined after application of rFVIII products in a tail clip model using FVIII deficient mice.

Results

FVIII activity determination using four ChS FVIII activity and 15 OS clotting assay reagents demonstrated similar assay reagent-dependent trends for rVIII-SingleChain and the comparator products. Further, whereas the mean OS/ChS FVIII assay ratios were in the range of 0.87 to 0.91 for the rFVIII comparator products, rVIII-SingleChain resulted in a mean ratio of about 0.5. TG investigations using an activator reagent consisting of 1 pM tissue factor and phospholipids considered to reflect the physiologic conditions of vessel injury were performed. These showed that when applied based on the ChS assay, rVIII-SingleChain and the comparator products delivered comparable time to peak and thrombin peak results whereas when applied based on the OS assay, rVIII-SingleChain showed increased potency. Comparable results were obtained in a tail clip model of FVIII deficient mice. When dosed according to the ChS FVIII assay, rVIII-SingleChain and the comparator products resulted in comparable blood loss. But when blood loss was compared based on the OS clotting activity applied, rVIII-SingleChain was associated with reduced blood loss.

Summary – Conclusion

Despite different OS/ChS assay ratios, rVIII-SingleChain and the rFVIII comparator products investigated showed comparable trends using 15 OS clotting reagents. In addition, the application of a global coagulation assay (TG) and an in vivo hemostasis model demonstrated that the ChS FVIII activity assay best reflects the "true" (= physiologically relevant) potency of rVIII-SingleChain when compared to other rFVIII products.

P09
CONGENITAL AFIBRINOGENEMIA AND PULMONARY THROMBOEMBOLISM TREATED WITH ENOXAPARINE AND DIRECT ORAL ANTICOAGULANTS

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Introduction

Congenital afibrinogenemia belongs to the group of autosomal recessive bleedings disorders and represents the absolute deficiency of fibrinogen. Patients with afibrinogenemia can, despite the absence of fibrinogen, they suffer bleeding or both venous and arterial thromboembolic disease.

The relationship between afibrinogenemia and thrombosis has been debated and poorly documented in the literature.

Case

A 34-year-old woman diagnosed with congenital afibrinogenemia and contraceptive hormonal treatment with a long-term bleeding history: autolimietd joint bleeding treated with fibrinogen concentrates (FC), right adrenal hematoma and intracerebral bleeding without sequelae in august 2013.

She was admitted to her community hospital complaining of right chest pain. A CT scan was performed and a pulmonary thromboembolism in the right lobar artery was diagnosed. She was treated with fibrinogen concentrates to maintain fibrinogen levels above 100 mg/dL and started bemiparin 5000 units /day. She was discharged, and a month later a new control CT scan was done, detecting the persistence and the increase of the artery thrombus. The patient was admitted in our Hospital, and started anticoagulation treatment with enoxaparin 60 mg/kg bid and cryoprecipitate (due to a fibrinogen concentrates shortage at our hospital at that moment) to maintain levels of fibrinogen above 100 mg/dL. After a multidisciplinary meeting with cardiovascular surgery, we decided to continue with anticoagulation treatment with enoxaparine 60 mg/kg bid, maintaining levels of anti-Xa between 0.5-0.7 UI/mL and a prophylaxis treatment with fibrinogen concentrates 3 grs every other day, to maintain levels between 70-150 mg/dL.

After two years with this treatment, due to elevated risk of osteopenia related to heparin and patient preference, we decided to switch enoxaparine to apixaban 2.5 mg bid.

Conclusions

Patients with congenital afibrinogemia and thrombotic events may beneficiate with use of direct oral anticoagulants and concomitant prophylaxis treatment with fibrinogen concentrates. This could be a safe alternative of anticoagulation treatment for these patients.

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P10
FACTOR XIII DEFICIENCY IN A PATIENT WITH GORHAM-STOUT DISEASE

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Background

Gorham's disease (GD) is a rare genetic disorder occurring in children and young adults characterized by resorption of flat bones and localized lymphangiogenetic proliferation. Surgical resection is one of different treatment modalities currently existed. Acquired coagulopathy is sometimes a complication of vascular tumors, particularly after surgery. Factor FXIII deficiency is also an inherited rare genetic disorder that causes severe hemorrhage particularly after trauma or surgery in the homozygous patients.

Aim

We report here a case of patient with Gorham's disease with excessive bleeding after surgery, who discovered with moderate factor XIII deficiency, successfully treated with Factor XIII infusion.

Methods

A 24-years man with Gorham's disease was admitted to orthopedic department of our hospital in February 2016, due to stiffness on right knee where a prosthesis had been located several years before. He presented with giant hemangioma extending from right paravertebral tissues, to gluteus and femur. In order to mobilize the knee the patient underwent to surgery with epidural analgesia. Bleeding from site of spinal injection started after few days and large hematoma therefore drained. New bigger paravertebral hematoma developed some days later, with severe anemia that required blood transfusion and admission to intensive care unit. Coagulation exams showed mild prolongation of PT and aPTT (1.2 and 1.25 respectively), mild reduction of fibrinogen (150 mg/dL), elevation of D-dimer (5000 ng/mL), with severe reduction of FXIII sub A (5%). A picture of mild intravascular disseminated coagulation with factor XIII deficiency was recognized.

Factor XIII (Cluviat, 25 U/Kg) were infused, initially every 72 h and subsequently weekly to maintain FXIII levels above 50%. The parents were tested for factor XIII level and they resulted normal, thus a new mutation in the patient was supposed.

Results

At the beginning, FXIII levels maintained below 30% although weekly infusion of Cluviat and bleeding from surgical wound continued. Clinical condition and bleeding started improving only after two months of continuous treatment when the paravertebral hematoma slowly reduced and factor XIII level increased with longer need of infusion. Finally, surgical wound healed by third intension. Currently the patient restores mobilization, hemoglobin level is within normal range (14.5 g/dl) and coagulation parameters are stable (PT 1.05, aPTT 0.93, fibrinogen 150 mg/dl, d-dimer 3000 ng/ml). Factor XIII level is actually 45% and no further infusion has been necessary for three months. Patient is now continuing the follow up with check of coagulation parameters every month.

Conclusiona

We have reported a case of patient affected with Gorham's disease and Factor XIII deficiency, both rare disorders never described in association. We suppose that excessive bleeding after surgery probably sustained by prior factor XIII deficiency caused an acquired coagulopathy with further consumption of factor XIII and worsening of bleeding in a vicious cycle. Treatment with Cluviat was efficacy in stopping bleeding, repairing surgical wound and restoring factor level approximately around 50%.

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P11
IMMUNE THROMBOCYTOPENIC PURPURA ASSOCIATED WITH FINGOLIMOD

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Background

Fingolimod is an oral sphingosine-1-phosphate–receptor modulator which causes lymphocyte sequestration in lymph nodes. It was approved for relapsing Multiple Sclerosis (MS) following evidence it reduced relapse rates by 50%[1,2]. The Therapeutic Goods Administration (TGA) of Australia as of September 2015 was aware of only one case where fingolimod preceded ITP by five weeks.

Aims

To report three cases of ITP associated with fingolimod.

Methods

We retrospectively reviewed three cases of fingolimod associated ITP who presented to Monash Health between 2013 and 2015.

Results

Cases are described in Table 1. None were on any medications known to cause ITP and routine investigations were non-contributory. All cases were treated with immunosuppression. Case 1 successfully weaned prednisolone after fingolimod cessation whilst case 2 had a slower wean whilst continuing fingolimod therapy. Case 3 had more refractory ITP and re-exposure to fingolimod worsened thrombocytopenia.

Possible mechanisms of the potential association between fingolimod and ITP remain unclear. One possible theory is immune dysregulation given fingolimod has been associated with autoimmune haemolytic anaemia[3] and haemophagocytic syndrome[4,5]. Another could be that it merely highlights autoimmune clustering.

Table 1.

	Case 1	Case 2	Case 3
Year at ITP Diagnosis	2014	2013	2015
Age (years)	22	51	59
MS Duration (years)	3	2	10
Previous MS Therapy	Beta interferon	Beta interferon	Methylprednisolone, Dimethyl fumarate
Other Autoimmune Conditions	-	Rheumatoid Arthritis Graves' Disease	-
Duration of Fingolimod prior to ITP	12 months	2 months	19 months
Fingolimod post ITP	Continued	Continued	Discontinued
ITP Treatment	Prednisolone	Prednisolone, IVIG, Azathioprine, Hydroxychloroquine	Prednisolone, IVIG, Azathioprine, Hydroxychloroquine, Elthrombopag, Romiplostim

Summary and Conclusion

In conclusion, our cases highlight that clinicians should be aware of the possible association between ITP and fingolimod although the mechanism for this remains unclear.

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P12
LOCAL AUDIT INTO BLEEDING ON ANTICOAGULATION THERAPY AT NORTH WEST LONDON NHS TRUST

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Background

Anticoagulation therapy is the mainstay of treatment for many health conditions. This includes venous thromboembolic disease, atrial fibrillation and thromboembolism secondary to metallic heart valve replacement. Whilst anticoagulant therapy has been proven effective in such conditions, they do carry significant morbidity and mortality, particularly in the form of acquired bleeding tendencies.

Historically, the mainstay of treatments has been with courmarins and unfractionated heparin. This changed following the introduction of low molecular weight heparin (LMWH), and subsequently with the development of direct oral anticoagulant medications (DOAC). Much evidence has been produced analysing the effectiveness of DOAC medications, and also their associated risks of bleeding. It remains important to note that experience of DOACs (and their novel reversal agents) is still limited, and many clinicians' experience is still lacking. Previous audits within our institution have shown LMWH to be associated with significant bleeding squeal when associated with renal impairment.

Aims

We wanted to determine the local rate of bleeding on different anticoagulation therapies and their management and outcomes. Particular focus would be on had the rate of bleeding on patients treated with LMWH with renal impairment.

Methods

We conducted a retrospective audit of 14 patients, presenting with acute bleeding whilst on anticoagulation therapy, over a 6-month period. We collected data from our referral list, medical notes, electronic records and our transfusion laboratory. Anticoagulant therapies reviewed included warfarin, LMWH, antiplatelet agents and DOACs.

We collected data on the bleeding site, reversal agents or blood products usage, renal function and finally mortality data.

Results

We present data on which bleeding sites were associated with different anticoagulant therapy, and which therapies were used in control of bleeding. We demonstrate a bleeding propensity for patients on anticoagulation therapy with impaired renal function, and also a high incidence of death. We also report a reduction in bleeding with LMWH following local changes in practice. The highest incidence of bleeding was observed in patients treated with warfarin.

Conclusion

Our local audit supports recent trial literature that patients treated with warfarin have a higher incidence of bleeding compared to novel agents. The significant reduction in bleeding on LMWH is likely secondary to staff education and training, in addition to implementation of new local protocols.

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P13
ADDRESSING A COMPREHENSIVE EFFICACY AND USE OF OCTAPLEX IN DISTRICT REGIONAL HOSPITAL: WHAT CAN WE IMPROVE IN OUR DAILY PRACTICE?

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Background

The use of prothombin complex concentrate (PCC) is indicated for patients for the emergency reversal of warfarin in life threatening major haemorrhage and/or emergency bleeding/surgery. Reversal of the anticoagulant effect of Warfarin is achieved immediately and completely with Octaplex. The use of PCC is complicated by risk inducing anaphylaxis and pro-thrombotic complication. This is also considered a high cost drug. The British Committee for the Standard in Haematology (BCSH) has provided extensive recommendation for PCC use.

Aims

To audit how closely BCSH guidelines on the use of PCC are being followed in Croydon University Hospital. Post implements intervention and re-audit was implemented to assess any change.

Method

All cases of Octaplex prescribed within the Trust from January 2015 to June 2016 were identified. The data was gathered from 30 cases during the first 12 months and cut off to 10 cases in the last 18 months using a *proforma* to select key information including identification of clinical indication, dose given, delay in treatment, warfarin reversal, source of bleeding, use of blood products, and administration of vitamin K and INR results.

Results

Octaplex was given appropriately in 85% of the cases initially audited. Vitamin K was used appropriately in 78% initially and there was no significant difference in the statistical analysis performed ($p < 0.01$).

Summary/Conclusion

Octaplex has been used for the right indication by the Trust under BCSH guidelines (98%). Intracranial Haemarraghes (ICH) and relation with INR results and potential complication was statistically significant STD [.6465] p 0.01. Despite this the INR was corrected (≤1.5) the average delay in getting INR results was 1 hour – 1 hour and 30 minutes and delay between releasing the PCC from blood bank to infusion.

Octaplex is effective in reversing the majority of patients' anticoagulation. Delay in initiating treatment for the reversal of VKA and adherence to protocols remained as a challenge. In re-audit assessment performed six months later the time frame for adequate administration was reduced to 45 minutes.

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P14
CHANGES IN PLATELET AGGREGATION DURING PREGNANCY AND THE IMMEDIATE POSTPARTUM PERIOD

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Background

Platelet dysfunction is implicated in uteroplacental disorders. During the early stages of gestation platelets have important roles in the process of placentation. Platelet function contributes to enhanced haemostasis at delivery. However, there is limited data on the changes of platelet function during normal pregnancy. Understanding physiological changes of platelet aggregation during different stages of pregnancy is helpful for better understanding of pathophysiology of abnormal placentation.

Aims

To assess platelet aggregation during three trimesters of pregnancy

and immediate postnatal period in normal healthy women compared to control non-pregnant group.

Design

Cross-sectional cohort study including a total of 46 women: 10 participants for each trimester, 10 postnatal cases and 6 control non-pregnant women. Case selection was based on specific inclusion criteria.

Methods

30 mL of venous blood was obtained from each participant following consent. Light transmission aggregometry was performed with Dual channel Payton 600B aggregometer using six platelet aggregating agonist (epinephrine, adenosine triphosphate, collagen, ristocetin, arachidonic acid and U46619).

Results

The findings included reduced secondary aggregation curve appearance in pregnant and postnatal women when compared to control group, which was most apparent in the third trimester. Compared to non-pregnant controls, platelet aggregation induced by ADP and collagen were reduced during third trimester while epinephrine induced aggregation was reduced during the first trimester.

Conclusion

Reduced platelet reactivity in response to epinephrine during early pregnancy can be considered as a mechanism to reduce thrombosis and allow normal placentation while diminished ADP and collagen induced aggregation in third trimester could be a compensatory mechanism since pregnancy associated with hyper-coagulation particularly in late stages.

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P15
DEFINING THE OPTIMAL TREATMENT SCHEDULE OF THROMBOPOIETIN RECEPTOR AGONISTS IN THE TREATMENT OF IMMUNE THROMBOCYTOPENIAS

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Background

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets. Pathophysiology of ITP is still under study, it involves platelet destruction and a relative platelet underproduction by bone marrow[1]. The new class of medications for ITP, called thrombopoietin receptor agonists (TRAs), stimulate megakaryocyte growth and increase platelet production. TRAs are currently administered as second line therapies of ITP[2], the definition of their optimal schedule is however still debated. It is well known that romiplostim determines a direct dose-dependent increases in platelet counts, however the dose required to elicit a platelet response varies between individuals. Guidelines recommend to administer romiplostim weekly; however, the optimal dose interval for romiplostim has been poorly explored[3,4].

Aims

Here we report our center's experience on the management of three adult Caucasian patients with refractory ITP successfully treated with biweekly administration of romiplostin.

Methods

Treatment was started with a weekly injection (1 mcg/kg), and the dose was escalated until a titrated dose was achieved to maintain platelet count> 50× 109/L ,at least for two consecutiveweeks. Patients were scheduled to a biweekly treatment and returned to a weekly administration in case of platelets count decrease to <30 × 109/L or in presence of active bleeding. All the patients were not-splenectomized and they had already received rituximab for previous ITP relapses.

Results

In one patient a weekly injection of 8 mcg/kg maintained platelet > 50 $x10^9$/L for one month , after the first month a biweekly administration of romiplostin was successfully continued for two years. Two patients achieved a platelet response with 3 mcg/kg and one with 4 mcg/kg. All them switched to a biweekly schedule after one month for stable platelet count. Platelets count of the first two patients fell to < 30 x 10^9/L after 4 and 2 months, respectively. All patients in our series responded upon treatment with romiplostin also when a weekly administration was required without bleeding. In the first case, a platelet response was achieved again with a dose of 5 mcg/kg, after one month, a biweekly schedule was again administered for seven months. The patient is currently treated with a biweekly treatment administration.

Conclusions

Our case series confirms the wide individual variation in the response to TRAs. In absence of identified factors that allow to predict these variations, attempts to prolong dose intervals should be made cautiously. TRAs treatment for ITP can be personalized.

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P16
IMMUNE THROMBOCYTOPENIA: AN EGYPTIAN EXPERIENCE IN MANAGING ADULTS

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Background

Idiopathic thrombocytopenic purpura (ITP) is a heterogeneous clinical disorder characterized by immune-mediated platelet destruction. The clinical differences between newly diagnosed and chronic ITP suggest the existence of different pathophysiological mechanisms in the two forms**.** We aimed to study the clinical, laboratory parameters as well as response to therapy in Egyptian adults with ITP.

Methods

We investigated 150 Egyptian patients with ITP who were registered in clinical hematology unit, Cairo university, Egypt during period between 2008 and early 2016 through history, physical examination, laboratory tests including CBC, reticulocyte ounts, ESR, PTT, PT, virology markers; CMV IgM, EBV IgM, HCVAb, HBsAg and HBcAb, ANA, Lupus anticoagulant, anticardiolipine, H pylori antigen in stool and TSH and response to therapy including response to rituximab and thrompopoietin agents recently introduced as line of therapy in our center.

Results

We had investigated 150 ITP patients, Female (*n*;123) were 82% while

male were 18%, The median age at the time of diagnosis was 30 years and its range was (14–70) years, Duration of disease ranged between (3 months-21 years) where the median duration was 2.5 years, 45% were newly diagnosed, 44% had chronic ITP and 10% had persistent ITP. Bleeding symptoms were present in 88% (the frequency of various bleeding symptoms were as follows: cutaneous bleeding 79%; gingival hemorrhage 33%; epistaxis 30.5%; vaginal bleeding 27.7%; melena 3.7%; hematuria 4.6%; 1.8% fresh bleeding per rectum and post-partum hemorrhage 0.9%), The median platelet count at the time of diagnosis was 15,000/ mm^3 where 38.8% patients had a platelet count <10,000/mm^3, ANA was positive in 13.8%, and anti-DNA was positive in 1.8% of ITP patients who had symptoms and signs fulfilling criteria to diagnose SLE. APL antibodies were positive in 4.8% who also had history either of thrombosis or abortion. HBsAg was negative in all studied patients where anti-HCV antibody was positive in 13.8% of patients, also 15.7% of our patients had positive H pylori antigen in stool with silent gastritis, 2.7% had positive anti EBV IgM with high titer and none of studied patients had positive anti CMV IgM. Regarding the thyroid functions 6.4% had abnormal functions where 3.7% of ITP patients had overt hypothyroidism. Also the onset of disease was related to pregnancy in 12% of ITP patients. Regarding Treatment and follow-up; There was an indication for treatment in 96% of patients, Of the 150 ITP patients who were given first-line therapy (corticosteroid 1 mg/kg/day PO), there was complete response (CR) in 40.3% and 59.7% patients were nonresponsive to therapy. Patients who had failure of response to 1st line of therapy were given a 2nd line of therapy and the details of it were as follow (splenectomy was done in 16,1% and CR was 3%, 20% received rituximab and CR was 60%, 3% received (TPO) agonist; Eltombopag and CR was 100%, 45% received combined azathioprine and steroid therapy and CR was 64%, 4.8% received triple therapy in form of steroid, azathioprine and danazole where CR was 66%, 8.1% received vincristine and CR was 20% and 5 patients received anti H pylori triple therapy and CR was 20%).

Conclusions

Most ITP patients were females and investigating 2ry causes of ITP cases even there is no clear symptoms of the 2ry cause is very important. Using another agents as 2nd line therapy rather than splenectomy they proved its efficacy.

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P17
QUALITATIVE COMPOSITION OF THE ACUTE STROKE AND POST STROKE PEPTIDE POOL FRACTIONS

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Background

As known ischemic stroke provoked irreversible changes in the organism and fully recovery has not observed[1,2]. Some reactivity of the haemostasis system was shown during the acute phase of ischemic stroke as well as post few years[3]. Here the idea was explored that index of organism endo-intoxication[4] such as peptide pool with Mr up to 5 kDa generated in the bloodstream during the acute phase and their presence past one year of stroke could provoke disease repetition.

Aim

To characterize qualitative composition of the acute stroke and post stroke PP fraction.

Methods

Fractions of peptide pool (PP) were separated from 10 ml of the blood plasma of each tested group: healthy donors, patients with atherothrombotic (AIS) and cardioembolic ischemic stroke (CIS) in acute phase of disease and the same patients one year past acute phase by the method of Nikolaichyk V[5]. Concentration was counted in respect to calibration chart and purity was controlled by 15% PAGE[6]. Qualitatively and quantitatively characterization of each separated PP fractions was performed by the size exclusion chromatographic on the Sephadex G-15 column[7]. The speed was 30 ml/hour. The column was calibrated by application of the standard markers solution.

Results

Ischemic stroke accompanied by the formation of the peptide pool with Mr up to 5 kDa. Stroke PP fractions were qualitatively and quantitatively differ comparing to healthy donor's PP faction. It was shown that concentration of acute AIS PP fraction was 3 times more higher and for acute CIS 2,5 times than healthy donor's PP fraction. One year past acute phase this correlation was close or identical to donors. Just one peptide with Mr about 1,32 kDa was presented in the healthy donor's PP fraction. The elution volume of this peptide was equal 1,1±0,1 pc. of the total column volume. The same but higher peak was noticed in the stroke PP fractions. Beside this stroke PP fractions include in average 7 peptides. Certain peptides specific for some stroke PP fractions were noticed. The fact is that peptide with Mr 2,95 kDa was typical just for the CIS PP fraction in acute phase as well as past one year. The buffer volume for elution of this peptide was 0,45 ± 0,05 pc. of the column volume. The peptide with Mr 1,45 kDa was typical just for acute AIS PP fraction. The elution volume of this peptide was 0,9 pc. The total area under the peaks was significantly bigger for the one year past acute AIS as well as CIS PP fractions. This value was equal 2631 and 3417 s.u. respectively. The analogical index for the acute stroke PP fractions was equal in averaged 1648 s.u. Healthy donor's PP fraction was characterized by the 263 s.u. of under peaks area.

Discussions

Despite the reduction in PP concentration over time, the year past acute PP fractions had more diverse qualitative composition comparing with acute phase PP fractions. We assumed that components of peptide pool forms complexes with receptors on the platelet membrane and blocked the normal physiological processes in this way. Also it is possible binding formation between PP fractions and other proteins or molecules in plasma which could lids to prevention of the right binding. Perhaps mechanism triggered by the competitive inhibition reactions.

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P18
ADVERSE PREGNANCY OUTCOMES AND INHERITED THROMBOPHILIA-IS THERE A LINK? PERSPECTIVE FROM DEVELOPING COUNTRY

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Background
Familial defects and polymorphisms of clotting cascade proteins protein S, protein C, factor V Leiden G1691A and factor II G20210A are linked with increased risk of thromboembolism which is better known as inherited thrombophilia. Thrombophilia causes deep venous thrombosis, pulmonary embolism and is strongly associated with poor pregnancy outcomes. To date, there is limited data from our region on the role of these genetic abnormalities causing adverse pregnancy outcomes.
Aims
To determine the association of factor V Leiden G1691A and factor II G20210A with adverse pregnancy outcomes
Methods
It was a case control study, conducted at section of haematology, and PCR-RFLP technique is used at multidisciplinary laboratory, Aga Khan University Hospital. Females with adverse pregnancy outcomes who came to obstetrical clinic were included in the study as cases. Adverse pregnancy outcomes included recurrent pregnancy loss (defined as > 2 first trimester miscarriages or one or more second trimester miscarriage), severe pre-eclampsia, placental abruption, intrauterine growth restriction and still birth. Control samples are selected from females with ≥ 2 consecutive normal pregnancies. Calculated sample size is 172 which comprised of 86 cases and 86 controls.
Results
Overall mean age of all subjects was 28.5 years (±4.9). Mean age of cases was 29.3 (±5.17) years and of controls was 27.6 years (±4.5). 73 (84.8%) cases had recurrent pregnancy loss, 12 (13.9%) had pre-eclampsia, 8 (9.3%) had IUGR while placental abruption and still birth was present in 2 (2.3%) cases each. 10 (11.6%) cases had more than one adverse pregnancy outcomes. 19 (22.09%) cases had > 4 pregnancy losses. Among cases, 40 (46.5%) females had previous live births and 9 (10.4%) were pregnant at the time of sample collection. Two cases with recurrent pregnancy loss (p=0.155 OR=0.49) showed heterozygous mutation of factor V Leiden G1691A and while no mutation identified in the control arm. Heterozygous prothrombin gene mutation was identified in one case with recurrent pregnancy loss (p=0.316 OR=0.497) while none of the control exhibited this mutation
Summary/Conclusion
This is a small sample sized study which does not support a significant association between inherited thrombophilia mutations and adverse pregnancy outcomes. Apparent lack of association may be reconciled by the low numbers of subjects recruited.

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P19
ABSTRACT WITHDRAWN

P20
PLATELETS AGGREGATION UNDER THE INFLUENCE OF IGG SEPARATED FROM THE BLOOD PLASMA OF STROKE PATIENTS

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Background
Often immunoglobulin class G (IgG) appeared and circulated in the patient's bloodstream after disease including cardiovascular. Elevation of the IgG concentration after ischemic stroke was proved previously. Moreover IgG ability to induce releasing from the platelets granules of the certain proteins, fragments and protein complexes was showed in our last research[1]. It is well known that interaction between IgG and platelets surface causes modulation of the cellular response[2-3].
Aim
Was to investigate the healthy donor's platelets aggregation under the influence of IgG separated from the patients with ischemic stroke in the acute stroke as well as year past acute phase of ischemic stroke.
Methods
Blood plasma samples were taken from 35 healthy donors and 66 patients with atherothrombotic ischemic stroke (AIS) and 56 patients with cardioembolic ischemic stroke (CIS) during the acute phase of disease; 57 patients with AIS and 57 patients with CIS one year past acute phase of stroke. IgG was separated from the blood plasma by affinity chromatography[4]. All separated fractions of IgG were freeze-dried (LyoQuest, Spain), dissolved in vehicle and brought to concentration 300 mkg/mL. ADP-induced platelet aggregation was performs according the standard protocol during the first 2 hours after healthy donor's blood collection on the photo-optical aggregometer AT-02 (Medtech, PF)[5]. Control platelets aggregation sample included equal volume of vehicle instead of IgG. Statistical processing of the data was done.
Results
Has been shown impact of IgG was characterized by one-wave irreversible ADP-induced platelet aggregation. The influence of the IgG fraction separated from the healthy donors was equal to the control platelets aggregation. The maximum aggregation was shoved under influence of IgG fraction separated from the patients with AIS. This influence was on the 15% more intensive in comparison with influence of IgG fraction separated from the healthy donors. One year past disease all tested IgG fractions provoked inhibition of platelets aggregation up to 25%. The maximum inhibition of ADP-dependent healthy donor's platelets aggregation was provided by fraction separated from the patients with AIS one year past acute phase.
Conclusions
Atherothrombotic and cardioembolic ischemic subtypes of acute stroke accompanied by increased concentrations of immunoglobulin class G. All investigated IgG fractions separated from the stroke patients are able to influence certain parts of the haemostasis system instead of the IgG fraction separated blom the healthy donor's blood plasma. In particular IgG separated from the plasma of patients with AIS and CIS in the acute phase have caused the activation of ADP-induced healthy donor's platelets aggregation. In contrast, IgG separated from the plasma of patients with AIS and CIS one year past acute phase have caused inhibition of healthy donor's platelets aggregation. Results could be an evidence of the potentially different immunoglobulin fractions formation in the bloodstream of the patients with different pathology.

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INTRACRANIAL BLEEDING: SHOULD WE BRING HAEMOSTASIS INTO THE LIMELIGHT?

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Background/aim

Intracranial bleeding (IB) is a major cause of death and results from a wide spectrum of disorders. Although acquired coagulation alterations derived from antithrombotic therapy is one of the leading causes, other bleeding disorders could also contribute to this entity. Our aim was to describe the clinical profile, etiology and management in patients diagnosed with IB in a tertiary hospital.

Methods

A retrospective analysis was performed of a consecutive patient series, 18 years and above, with an IB diagnosis in our center from the 1st of January to 30th of June 2015. We studied demographic characteristics, clinical presentation, etiology, treatment strategies and outcome.

Results

A total of 213 patients were included in the statistical analysis; out of which, 122 cases (57%) were male and median age at presentation was 72 (29-96). The most frequent localization was intraparenchymal (35.6%), followed by subdural (30.9%) and subarachnoid (24.4%). Almost all patients were diagnosed by CT. Initial clinical presentation was heterogeneous, headache being the most common finding in the subarachnoid cohort, loss of consciousness in subdural cases and focal neurological signs in the intraparenchymal subgroup. Only an 11% had previous history of bleeding. Additionally, less than half (46%) received antithrombotic treatment, of which 38% were with acetylsalicylic acid 100 mg (ASA), 34% with a vitamin K antagonist (two-thirds of which were within therapeutic range) and 5% with DOACs. Primary prevention was the reason for 25% of the patients treated with ASA. We would like to highlight that 28% of these patients received antithrombotic reversal agents. With regards to the etiology, 35% was due to head trauma, 10% of aneurysm or vascular malformation, 29% of unknown cause and 7% due to antithrombotic therapy without previous trauma. Initial blood workup was altered without cause in 4.7% of patients, showing thrombopenia and elongated PT and aPTT. Although further studies were not conducted to determine the etiology of these findings. There was a 23% mortality of the cases studied.

Conclusions

In our cohort IB occurs mostly in head trauma injuries. Although almost half of them were on antithrombotic treatment, only some cases received reversal agents. Idiopathic haemorrhagic events and those with basic altered coagulation testing were not referred for further bleeding disorder advisement, bringing about the question of whether it's worth testing for causes of congenital or acquired bleeding diathesis.

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EUROPEAN HEMATOLOGY ASSOCIATION

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